CLINICAL THERAPEUTICS

Biventricular Pacing

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

A 55-year-old man who had had an anterior-wall myocardial infarction six months previously is admitted with an exacerbation of congestive heart failure. An electrocardiogram shows sinus rhythm with a left bundle-branch block; an echocardiogram demonstrates a left ventricular ejection fraction of 25 percent. He is treated with furosemide, lisinopril, and carvedilol. However, during an office visit three months later, he reports persistent shortness of breath with mild exertion. He is referred to a cardiologist, who recommends implantation of a biventricular pacemaker.

THE CLINICAL PROBLEM

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One quarter to one third of patients with heart failure have left bundle-branch block.[1-3] In an Italian series of 5517 outpatients with heart failure, 25 percent had left bundle-branch block.[2] An analysis of data on 2708 patients with moderate-to-severe heart failure participating in the Beta-Blocker Evaluation of Survival Trial (BEST) showed that 34 percent of the men and 23 percent of the women had left bundle-branch block.[3]

Patients with heart failure who have left bundle-branch block have a poorer prognosis than those without left bundle-branch block. In the series of Italian patients, the rate of death from any cause at one year was 16.1 percent for those with left bundle-branch block and 10.5 percent for those without it (hazard ratio for death, 1.70; 95 percent confidence interval, 1.41 to 2.05). The risk of sudden death was likewise significantly higher at one year among those with left bundle-branch block (7.3 percent vs. 4.9 percent; hazard ratio, 1.58; 95 percent confidence interval, 1.21 to 2.06).[2] Other studies have reached similar conclusions.[1,4]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Electrical depolarization is normally initiated throughout the cardiac ventricles by the His–Purkinje system (Fig. 1A and 1B). In patients with left bundle-branch block, conduction of the wave of depolarization in the left ventricle is markedly altered, proceeding from the anterior septum through the left ventricular myocardium to the inferior and lateral left ventricular walls (Fig. 1C).[5,6] As a result, left ventricular contraction is dyssynchronous, with the interventricular septum contracting before the left ventricular free wall.[7-9] Dyssynchronous contraction is mechanically inefficient, leading to decreases in the left ventricular ejection fraction (LVEF) and cardiac output.[10]

These observations led to the concept that simultaneous pacing of both the left and right ventricles (biventricular pacing) to resynchronize ventricular contraction (cardiac-resynchronization therapy, or CRT) might be beneficial in patients with

heart failure. With biventricular pacing, separate pacing leads are placed to stimulate the right and left ventricles, with pacing through each lead timed to coordinate electrical activation (Fig. 1D, **and the interactive graphic available with the full text of this article at www.nejm.org**). The right atrium is also paced, with a short atrioventricular pacing delay to ensure consistent pacing of the ventricles. The effect of biventricular pacing is lost if sinus beats reach the ventricles through the native conduction system.

Although biventricular pacing does not restore the physiologic conduction pattern, it eliminates the delay in electrical activation of the left ventricular free wall.[7] The duration of the QRS interval on the surface electrocardiogram tends to decrease with biventricular pacing,[11] although this effect is variable and does not appear to correlate well with the improvement in systolic function.[12] Mechanical rather than electrical synchrony appears to be the crucial factor in achieving a benefit.[7,13]

Hemodynamic responses to biventricular pacing include an increase in the rate of rise of left ventricular pressure, as well as increases in pulse pressure, left ventricular stroke work, and cardiac index and a decrease in pulmonary-capillary wedge pressure.[12,14,15] Echocardiographic studies demonstrate that the magnitude of mitral regurgitation is reduced.[16] Remarkably, CRT improves ventricular function without increasing myocardial energy consumption, in contrast to the effect of inotropic agents such as dobutamine.[17,18] In addition, CRT may reverse left ventricular remodeling over time.[19,20]

CLINICAL EVIDENCE

The initial randomized trials of CRT involved no more than 500 patients and lasted less than one year.[21-25] These trials enrolled patients with New York Heart Association (NYHA) class III or IV heart failure, with other requirements typically including sinus rhythm, an LVEF of 35 percent or less, and a QRS interval of at least 120 msec. These trials confirmed that the physiological effects of CRT were associated with increases in functional capacity and improvements in the quality of life. Such changes could be demonstrated as early as one month after the device was implanted.[24]

Two subsequent trials, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization–Heart Failure (CARE-HF), evaluated the effect of CRT on survival.[26,27] As in most of the earlier trials, enrollment criteria included sinus rhythm, an NYHA class of III or IV, an LVEF of 35 percent or less, and a QRS interval of at least 120 msec. In both trials, the risk of death from any cause was reduced by CRT as compared with no pacing; this difference was not significant in the COMPANION trial (hazard ratio, 0.76; $P=0.06$), but it was significant in the CARE-HF study (hazard ratio, 0.64; $P<0.002$).

CLINICAL USE

The indications for CRT include dilated cardiomyopathy (ischemic or nonischemic), an LVEF of 35 percent or less, a QRS interval of at least 120 msec, and NYHA class III or IV heart failure despite optimal medical therapy.[26,27] Optimal medical therapy should include at least loop diuretics for volume overload, a beta-blocker, and an angiotensin-converting–enzyme inhibitor or angiotensin II–receptor blocker.[28] Increased risks of bleeding or infection are relative contraindications, as is the presence of any other major life-limiting medical condition, such as advanced cancer. It has been suggested that patients whose heart failure is severe enough to require parenteral inotropic therapy should not receive a biventricular pacemaker.[6] Candidates for CRT may need a device with both cardiac-resynchronization and cardioverter–defibrillator functions; most candidates for biventricular pacing are also candidates for a defibrillator.[29]

The implantation of a biventricular pacemaker requires a method for pacing the left ventricle. In the standard approach, a specifically designed pacing lead is inserted into the mouth of the coronary sinus (in the right atrium) and advanced posteriorly around the atrioventricular-valve ring. The lead is then passed into a venous branch running along the free wall of the left ventricle (Fig. 1D).[30] In some patients, the left ventricular electrode cannot be properly positioned through the coronary sinus; minimally invasive thoracic surgical techniques have been used for lead placement in such patients.[31]

No specific preparation is required before the implantation of a biventricular pacemaker. A patient receiving anticoagulation should have such therapy withheld and a normal coagulation pro-

file documented. Implantation is performed by a cardiologist or cardiac surgeon with the patient under local anesthesia. After the pacemaker has been implanted, some patients report symptomatic improvement almost immediately, although it is unclear how much of this effect is psychological. As noted above, in clinical trials, objective evidence of functional improvement has been documented as early as one month after implantation.[24] An electrocardiogram is obtained to document the new baseline appearance with pacing. Care of the incision site used for the implant is similar to that for other pacemakers.

Patients who receive a biventricular pacemaker must undergo periodic clinical evaluation as well as have the device evaluated by a cardiologist with expertise in CRT management. Lead impedance, device programming, and battery life are all checked on a regular basis. In addition, however, some functional features of the device can and should be assessed by all clinicians caring for the patient. These include, in particular, an evaluation for symptoms of heart failure and electrocardiogram review. If the patient has had no improvement in functional status for the first month after implantation, the device may not be functioning properly or the programming of the device or lead position may not be optimal. Likewise, if after a period of clinical improvement, the patient has a sudden worsening of symptoms, the function of the device should be reassessed. The electrocardiographic findings should typically remain unchanged from the post-implantation baseline findings, with pacing artifacts present for all QRS complexes. Complete loss of the pacing artifact is unusual with biventricular pacemakers, since the two separate ventricular leads rarely fail simultaneously. Instead, lead disruption or malfunction, which is seen more often with the left than with the right ventricular lead, may be evidenced by widening of the QRS complex with or without a clinically significant shift in the QRS axis.[32] However, it is not always possible to recognize loss of left ventricular pacing from the surface electrocardiogram alone.

As with all permanent pacemakers, replacement of the pacemaker pulse generator is routinely required when the battery reaches the end of its service life, usually after four to seven years, depending in part on whether the device includes a defibrillator. In contrast, the pacemaker leads are usually permanent, provided that they are functioning properly. Lead extraction (because of fracture, loss of insulation, infection, or malfunction) may be difficult, especially if fibrosis of the pacing site has occurred. During extraction of the left ventricular lead there is a risk of coronary-sinus laceration. However, reports from institutions with experience in lead extraction demonstrate that the procedure can be performed safely.[33,34]

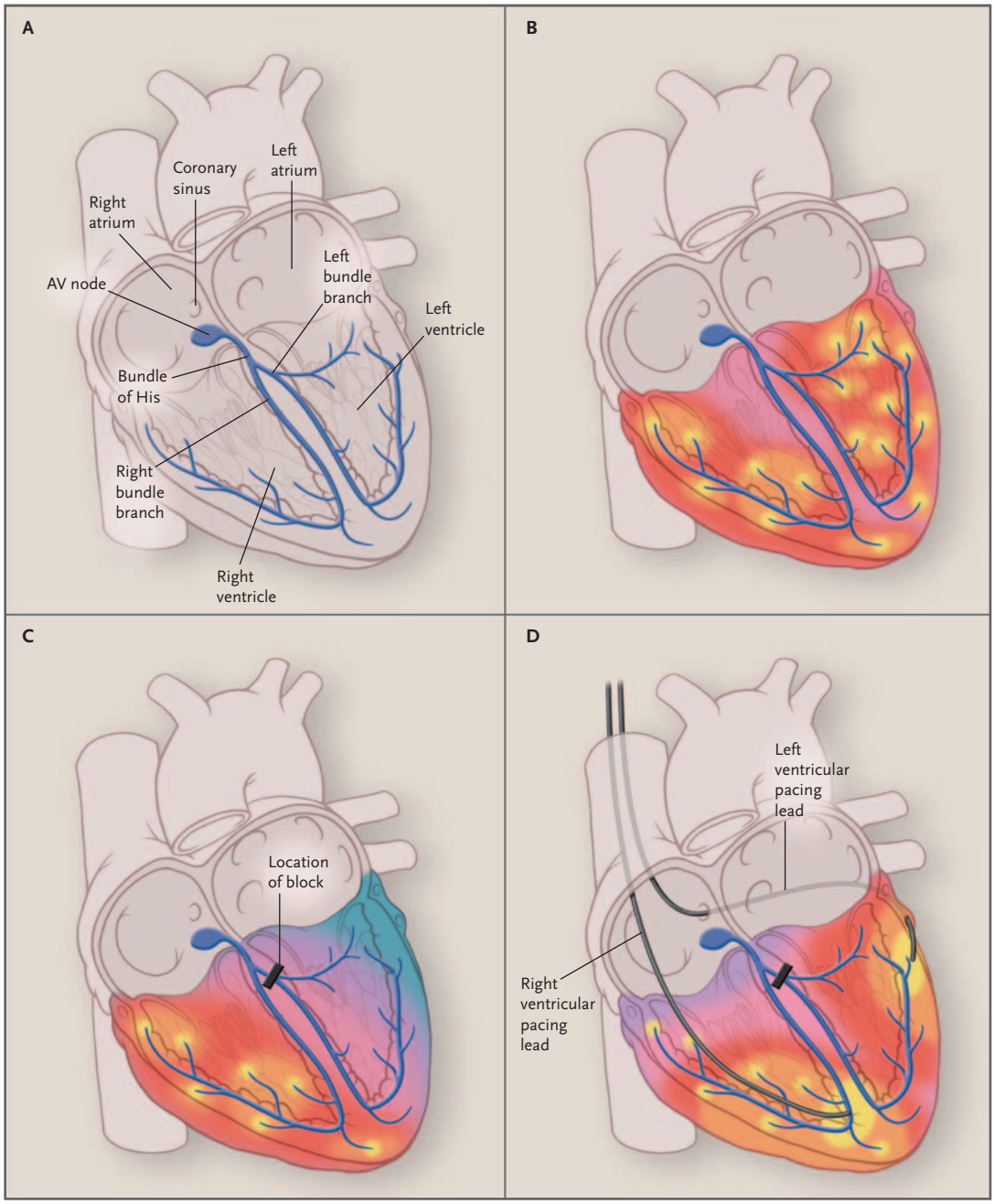
In the long term, CRT may be discontinued if no clinical benefit is evident or if complications associated with the device occur. Complications can include lead failure, device infection, and atrial dysrhythmias, with device tracking of the atrial rate. In one study, temporary interruption of biventricular pacing was quite common, occurring in 36 percent of patients by 2.5 years after implantation.[35] In most cases, it was possible to reinitiate biventricular pacing after correction of the specific problem.

Figure 1 (facing page). The Cardiac Conduction System and Biventricular Pacing.

The cardiac conduction system is designed to initiate depolarization of the cardiac ventricles widely and synchronously. Panel A shows the anatomy of the system, with the locations of the atrioventricular (AV) node, the bundle of His, and the right and left bundle branches. With normal conduction, the left and right ventricles are depolarized simultaneously, with consequent simultaneous contraction (Panel B). In Panel B, yellow areas are the sites of earliest depolarization (at the terminal ramifications of the conduction system), with successive regions of depolarization shown in orange, red, and pink. In the setting of left bundle-branch block, the right ventricular free wall and the interventricular septum are depolarized rapidly (Panel C). There is a clinically significant delay in the depolarization of the left ventricular free wall. As a result, left ventricular contraction is dyssynchronous. In Panel C, the sites of earliest depolarization are yellow and are all in the right ventricle; successive regions of depolarization are shown in orange, red, pink, purple, and blue. With CRT, pacemaker leads are situated to stimulate both ventricles, thus bypassing the conduction block in the left bundle branch (Panel D). Simultaneous depolarization and simultaneous contraction of the ventricles is restored. In Panel D, the sites of early depolarizations are yellow and are near the tip of both pacemaker leads as well as in the branches of the normally conducting right bundle-branch system. Successive regions of depolarization are shown in orange, red, pink, and purple.

ADVERSE EFFECTS

The most common problem encountered with CRT is the inability to implant the left ventricular



lead successfully, usually because of unfavorable coronary venous anatomy. Proximity to the left phrenic nerve, and the resulting uncomfortable diaphragmatic stimulation during pacing, also limits the number of acceptable pacing sites in some patients. In a systematic review that included all the major trials except the CARE-HF trial, the device was successfully implanted in 90 percent of attempts.[36] In the CARE-HF trial, implantation was successful in 97 percent of patients, although in 10 percent, more than one attempt was necessary before the procedure was successful.[27]

More serious complications have also been reported during the implantation of a biventricular pacemaker. In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE), COMPANION, and CARE-HF trials, coronary-sinus dissection occurred in 0.3 to 4.0 percent of patients and coronary-vein or coronary-sinus perforation occurred in 0.8 to 2.0 percent.[24,26,27] Perforation of the coro-

nary venous system can result in hemopericardium with tamponade; such sequelae were reported in less than 1 percent of patients in these trials. Other complications included pneumothorax, complete heart block, and asystole. In the systematic review cited above, the rate of periprocedural death was 0.4 percent (13 of 3245 patients).[36]

Dislodgment of the left ventricular pacing lead is a frequent problem after successful implantation of a biventricular pacemaker, occurring in nearly 10 percent of patients.[27,36] As described in the Clinical Evidence section, the most common consequence of the loss of left ventricular pacing is exacerbation of heart failure. Infection of the device, usually of the pacemaker pocket, and the development of atrial arrhythmias have been noted.

External electromagnetic fields may interfere with the function of pacemakers, and all patients should be warned about this possibility.[37,38] Such interference can be induced by cellular telephones, electronic security systems, and industrial equipment such as power cables and electrical motors. Potential sources of interference in the medical setting include magnetic resonance imaging, therapeutic use of electric current (e.g., electrocautery, cardioversion or defibrillation, and transcutaneous electrical nerve stimulation), and therapeutic radiation.

AREAS OF UNCERTAINTY

Several areas of uncertainty remain. It has not been established whether CRT is beneficial in patients with mild heart failure (NYHA class II), since only two small trials have included such patients.[23,39] In these analyses, CRT did not significantly improve functional status or the quality of life, although it did increase left ventricular volumes and, in one trial, LVEF. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) and the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial will evaluate the role of implantable cardioverter–defibrillators with or without CRT in large cohorts of patients with NYHA class I or II heart failure.

CRT does not result in significant clinical improvement in 20 to 30 percent of patients.[13,40] Although there may be various explanations for this observation, it has been suggested that an increased QRS interval may not be the best criterion for benefit from CRT. In several small, uncontrolled studies involving patients with wide QRS complexes, echocardiographic evidence of ventricular dyssynchrony was more predictive of benefit from CRT than was the duration of the QRS interval.[13,41,42] It has therefore been proposed that guidelines for the selection of candidates for CRT should suggest the use of echocardiography to identify dyssynchrony.[40] However, none of the major clinical trials of CRT used echocardiographic measures of dyssynchrony as the principal criteria for enrollment. Furthermore, it is not clear which echocardiographic variables should be used to select candidates for CRT.

The benefit of CRT in patients with atrial fibrillation has not been extensively investigated. A number of small studies (fewer than 200 patients) suggested that CRT improved functional capacity and the quality of life in these patients.[43-47] In most cases, ablation of the atrioventricular node was performed to ensure complete control of ventricular activation.

GUIDELINES

The 2002 joint guidelines of the American College of Cardiology, the American Heart Association, and the North American Society of Pacing and Electrophysiology endorse the use of CRT in patients with medically refractory, symptomatic, NYHA class III or IV disease and a QRS interval of at least 130 msec, a left ventricular end-diastolic diameter of at least 55 mm, and an LVEF of 30 percent or less.[48] Similar recommendations have been made by the Canadian Cardiovascular Society[49] and the European Society of Cardiology.[50]

These guidelines were refined by an April 2005 American Heart Association Science Advisory,[28] which stated that "optimal candidates for CRT have a dilated cardiomyopathy on an ischemic or nonischemic basis, an LVEF ≤0.35, a QRS complex ≥120 ms, and sinus rhythm, and are NYHA functional class III or IV despite maximal medical therapy for heart failure."

RECOMMENDATIONS

The patient described in the vignette meets all the recommended criteria for CRT: he has an ischemic cardiomyopathy with an LVEF of 35 percent or less and sinus rhythm with a left bundle-branch

block (by definition, with a QRS interval of at least 120 msec). I would make certain that his medical therapy is optimal. If he has any evidence of volume overload on physical examination, his furosemide dose should be increased and his doses of lisinopril and carvedilol should be increased to the maximum tolerated (or to a maximum of 40 mg once daily and 25 mg twice daily, respectively). If he remains symptomatic (NYHA class III or IV) despite this regimen, he should receive a biventricular pacemaker. Since this patient also satisfies criteria for the implantation of a cardioverter–defibrillator,[26,29,51] he should receive a device with both capabilities.[28]

No potential conflict of interest relevant to this article was reported.

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CORRECTION

Biventricular Pacing

Biventricular Pacing . On page 292, the sentence beginning 15 lines from the bottom of the left-hand column should have read, ``In these analyses, CRT did not significantly improve functional status or the quality of life, although it did decrease left ventricular volumes and, in one trial, increase LVEF,´´ not ``*increase* left ventricular volumes,´´ as printed. We regret the error.